Isoniazid Hepatitis Among Pregnant and Postpartum Hispanic Patients

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Synopsis

On request of local health officials, the authors investigated isoniazid (INH) hepatitis morbidity and mortality among patients attending an Hispanic prenatal clinic. Among 3,681 women treated with INH during and after pregnancy to prevent tuberculosis (TB), 5 developed INH hepatitis, and 2 of the 5 women died. Comparison with previously collected Public Health Service data concerning 3,948 nonpregnant women, using the Cox proportional hazards model, revealed a 2.5-fold increased risk of INH hepatitis in the prenatal clinic group. The mortality rate was four times higher in the prenatal clinic group. However, statistical power was low because of the small number of cases, and neither of these findings was statistically significant ($P > 0.05$).

In the absence of controlled studies, the issue of INH safety during the perinatal period remains unresolved. Nevertheless, current American Thoracic Society–Centers for Disease Control recommendations regarding TB screening, implementation of INH chemoprophylaxis programs, and adequate monitoring of individuals on INH should be adhered to. The results of this investigation raise concern that deviations from existing policy may contribute to unnecessary morbidity and mortality.

ISONIAZID (INH) PREVENTIVE THERAPY is recommended for persons infected with tubercle bacilli as indicated by a significant reaction to a tuberculin skin test. INH treatment is not without risks, however, and the recognition of INH-induced hepatitis more than a decade ago led to the recommendation that INH preventive therapy be restricted to those for whom the benefits appeared to clearly outweigh the risks (*1*). Although no special ill effects of INH on fetal development or maternal health have been documented (*2*), current guidelines adhere to the convention of avoiding unnecessary medication during pregnancy and recommend that INH preventive therapy generally be deferred until the postpartum period (*3*).

We report the results of a retrospective investigation requested by local health authorities after two women who were enrolled in a special prenatal tuberculosis (TB) prevention program died with fulminant liver disease.

Background

This investigation was carried out at a county clinic serving a 99 percent Hispanic population, including many recent immigrants from Mexico

and Central America who lived in crowded, substandard housing. Routine prenatal skin testing in 1980 revealed that 56 percent of the women had significant reactions (defined as > 5 mm induration by local protocol) to 5 TU PPD tuberculin administered by the Mantoux method. (The usual cutpoint for defining significant reactions recommended by the American Thoracic Society-Centers for Disease Control (ATS-CDC) is ≥10 mm induration (*1*).) Only 6 percent of the women who were referred for INH preventive therapy postpartum actually came to the clinic for this treatment. Because prenatal care provided more consistent contact with the health care system, in 1981 the clinic began a prenatal INH preventive therapy program for patients.

All prenatal patients had tuberculin skin testing on the first prenatal visit. Those who had significant skin test reactions with no evidence of active disease on chest radiograph were encouraged to begin INH after the first trimester of pregnancy. In the first 18 months of the program an average of 230 women per month were started on INH. Each was given a 3-month supply of INH at a daily dose of 300 mg, and then seen every 3 months for a followup interview until 12 months of medication had been dispensed. According to clinic policy, each woman was questioned about adverse reactions to INH at each followup interview. If a woman complained of any suspicious symptoms, a panel of liver function tests (LFTs) was obtained. Routine LFTs were not performed among asymptomatic patients.

Few side effects of any consequence were noted until the second half of 1982 when the two fatal cases of fulminant hepatitis occurred. As a result of these deaths, this retrospective study was undertaken at the request of local health authorities.

Methods

Possible cases of INH hepatitis among women enrolled during the first 18 months of the prenatal INH preventive therapy program were ascertained by reviewing records of the clinic, as well as records of the obstetrics and liver disease services at the largest county hospital, the discharge diagnoses of patients of all the county hospitals in the area, and the county health department records. We defined a possible case as a woman begun on INH during pregnancy who later developed symptoms of hepatitis and was found to have a serum glutamic pyruvic transaminase (SGPT) elevation more than four and a half times the maximum normal value, with no evidence to suggest viral or other toxic etiology.

No control group was available for comparison. Therefore, for a comparison group, data from nonpregnant women 15–44 years of age from the Public Health Service (PHS) multicenter INH Hepatitis Surveillance Study conducted in 1971–72 were used (*4*). In this comparison group, ethnicity data regarding Hispanic origin were not collected; 31 percent of the women in the comparison group were white, 50 percent were black, and 19 percent were of other races.

Possible cases of hepatitis from the prenatal clinic were submitted to the same panel of three experts that had evaluated the possible cases for the previous PHS study (*4*). Because this panel's members knew the nature of the investigation, a second panel of three different experts was convened. The second panel was blind to the nature of the investigation and received summaries of possible cases from the prenatal clinic group as well as from the PHS study. Because the two panels' final decisions differed somewhat, only those women from the 1981–82 study and the earlier PHS study who were judged to have INH hepatitis by *both* panels were considered cases for the purpose of our analysis.

In both study groups, the duration of INH treatment was determined for each woman. In the prenatal clinic group the number of months between starting and stopping treatment was tallied. It was assumed that all medication dispensed was taken except among women who were lost to followup, for whom 3 months were subtracted from the tallied treatment duration. In the PHS group the number of monthly followup visits was tallied, including only those months for which medication was dispensed and the patient returned for the subsequent visit.

To adjust for differences in age distribution and rates of followup between the two groups, risks of INH hepatitis were assessed using the Cox proportional hazards model (*5,6*); covariates were age and study group. Death rates per woman-years of treatment were compared by Fishers exact interval estimation (*7*).

Results

During the 18-month study, 3,681 women began INH during their prenatal care at the clinic. Of these, 1,030 never returned for followup. Forty-six percent of women completed 6 months of treatment; 16 percent completed 12 months of treat-

ment. By contrast, loss to followup was substantially lower in the PHS study. Of the 3,948 women starting treatment, 70 percent completed 6 months of treatment and 45 percent completed 12 months of treatment.

The age distribution of women in each study group is shown in table 1. As might be expected, ages of women in the prenatal clinic group were skewed toward the youngest age group (15-24), whereas ages of women in the PHS study group were more uniformly distributed among the three age groups.

In the prenatal clinic group, a total of eight possible INH hepatitis cases were identified, including the two index fatalities. Five of these were judged to be INH hepatitis by both expert panels (five by the original PHS study panel, six by the newly composed panel). All began INH therapy between the third and eighth month of gestation (mean = sixth month). Duration of INH administration before illness ranged from 2 to 7 months, with a mean of 4.4 months. Onset of symptoms occurred postpartum for three of the five women. In the PHS study group, the panels identified 10 cases (13 by the original PHS study panel, 10 by the newly composed panel). Duration of INH exposure before illness ranged from 2 weeks to 7 months, with a mean of 3.5 months.

Case rates per 1,000 woman-years of treatment for each study group, stratified by age, are shown in table 2. In both groups the case rates increased with age. In each age stratum the crude case rates were higher in the prenatal clinic group than in the PHS study group. Using the proportional hazards regression model to estimate a summary relative risk (*RR*) adjusting for age and differential followup, we found a two-and-a-half-fold increase in risk of INH hepatitis among the prenatal clinic patients relative to the PHS study group. However, this increased risk was not statistically significant at the $P < 0.05$ level (*RR* = 2.5, 95 percent CI = 0.8–8.2).

Two deaths from INH hepatitis occurred among women in the prenatal clinic population, and one death occurred in the PHS study, yielding mortality rates of 1.6 and 0.4 per 1,000 woman-years of treatment, respectively. This difference was not statistically significant (Incidence Density Ratio = 4.0, 95 percent CI = 0.2–258).

Both deaths of prenatal clinic women occurred postpartum, and both followed similar clinical courses. The first death was that of a 27-year-old Mexican immigrant who started INH in her eighth month of pregnancy. After 4 months of treatment

Table 1. Number of women of reproductive age prescribed isoniazid in two studies

Age group (years)	Prenatal clinic 1981–82		Public Health Service study 1971–72	
	Number	Percent	Number	Percent
15–24	2,083	57	1,269	32
25–34	1,361	37	1,217	31
35–44	237	6	1,462	37
All	3,681	100	3,948	100

Table 2. Cases of isoniazid hepatitis and case rates for two study groups of reproductive age women, by age group

Age group (years)	Woman-years on INH	Cases	Crude case rate[1]
	Prenatal clinic patients 1981–82		
15–34	1,171	3	2.6
35–44	88	2	22.7
	Public Health Service study, 1971–72		
15–34	1,727	1	0.6
35–44	1,035	9	8.7

[1]Per 1,000 woman-years of treatment.

(at 3 months postpartum) she presented with anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, and jaundice. Laboratory values showed serum glutamic oxalacetic transaminase (SGOT) 957, SGPT 1397, with negative hepatitis B studies (HBsAG, AntiHBc, HBeAg), and a negative hepatitis A virus (HAV) IgM fraction. The second case was that of a 24-year-old Mexican immigrant who began INH in her seventh month of pregnancy. After 7 months of treatment (at 5 months postpartum) she presented with anorexia, nausea, vomiting, fatigue, light stools, dark urine, and jaundice. Laboratory values showed SGOT 1230, SGPT 1980 with negative hepatitis B studies (HBsAg, AntiHBc) and a negative HAV IgM fraction. Neither woman had a history of intravenous drug use, recent foreign travel, blood transfusion, or exposure to jaundiced persons or toxins, and neither had evidence of chronic liver disease. Both women were hospitalized and treated for hepatic failure. Both developed encephalopathy and died with submassive hepatic necrosis and *Escherichia coli* sepsis.

The fatal case from the PHS study was that of a 38-year-old black woman who took INH for 5 months before presenting with nausea, vomiting, fever, malaise, dark urine, and light stools of 2 weeks duration. She had noted scleral icterus for several days. Her laboratory test values were SGOT

1650, SGPT 440, and Australian Antigen negative. She was hospitalized and died in hepatic coma.

Discussion

To our knowledge there have been no previous reports of INH-associated hepatitis in pregnant or postpartum women. In our comparison of the group that began treatment prenatally with previously collected data from nonpregnant women, we found a two-and-a-half-fold higher morbidity rate and a fourfold higher mortality rate among the women beginning treatment during pregnancy. The differences were not statistically significant, but the study had poor statistical power because of the small number of cases in both series.

Substantial differences between our retrospective study and the prospective PHS study may have biased the results toward diminishing the difference in disease rates between the two study groups. In the 1981–82 study, underascertainment of disease is likely to have occurred because we used a retrospective methodology in a mobile population with poor followup. Also, since the 1971–72 study, viral hepatitis serology has become widely available, allowing for more specific case determination in the contemporary investigation. Thus the relative lack of specificity in case classification in the earlier study may have led to a relative overestimation of the case rate in the historical comparison group, whereas underascertainment may have led to a relative underestimation of case rate in the prenatal clinic group. These biases would tend to result in a spuriously low relative risk.

The interpretive difficulties in comparing two investigations differing in time, demographics, and methodology serve to exemplify the need for prospective studies of drug toxicity in pregnant and nonpregnant Hispanic women, and perhaps Hispanic women compared with white or black women.

Nonetheless, there are theoretical reasons to believe INH could be more toxic during pregnancy. There is some evidence that pregnancy may predispose women to the more fulminant forms of some types of viral hepatitis (*8,9*), suggesting that the liver may be more vulnerable to infectious agents during pregnancy. In addition, pregnancy may alter the hepatic excretion of drugs (*10*) and increase vulnerability to hepatotoxins (*11,12*).

Our investigation provides no definitive evidence regarding the pregnancy-associated risk of INH hepatotoxicity, but the cases investigated do raise concern sufficient to underscore existing policy. ATS–CDC policy recommends that the perinatal use of INH chemoprophylaxis be avoided except among women at very high risk of tuberculosis, such as recent contacts of infectious cases (*3*). Although the study clinic treats larger numbers of pregnant women than any other known to us, offering INH chemoprophylaxis to pregnant women has apparently not been uncommon elsewhere (*13*).

To maximize the effectiveness of TB screening and chemoprophylaxis programs, they should be focused on persons at highest risk of developing active disease. Including low-risk persons (such as those with only a 5 mm reaction to PPD) can dilute the effort to control TB by expanding the size of the program, thereby running the risk of surpassing staff capacity to follow each person for compliance and for adverse reactions. Current ATS-CDC recommendations regarding followup of persons on INH include screening monthly for adverse reactions and dispensing no more than a 30-day supply of INH (*3*). Yet according to a recent survey, administering more than a 30-day supply of INH is still all too common (*14*).

The cases of hepatotoxicity reported in this article provide a reminder that serious illness and death may result from INH chemoprophylaxis. Current guidelines, developed to help avoid these outcomes, should be followed.

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Surveillance for Injuries: Cluster of Finger Amputations from Snowblowers

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Assisting in the data collection and analyses were Ms. Shelly Thomas and Mr. Mike Faust of the Oklahoma State Department of Health and the staffs of hospital emergency rooms in the Denver area. Dr. Richard Goodman of the Centers for Disease Control reviewed the manuscript and made substantive suggestions concerning it.

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Synopsis

In an investigation of the health effects of a Christmas eve snowstorm in 1982, a review of emergency room records in the Denver area identified a cluster of 17 cases of finger amputations. Fifteen (88) percent of these amputations were associated with snowblower use. An additional 12 persons with hand or finger injuries without amputations from snowblowers were identified. A case-control study was performed comparing these patients with a control group who had used snowblowers. Patients were more likely than controls to have had their machines become clogged with snow (odds ratio [OR], 3.4, 95 percent confidence limits [CL], 0.74-15.4). Using a hand to dislodge trapped snow was the only risk factor identified for the patients (OR, 116; 95 percent CL, 16-820). No differences were found for other variables such as type of snowblower, instruction for use, or previous experience using a snowblower.

The findings suggest that the most feasible measure to prevent such injuries is a change in snowblower design to preclude entry of a hand while the machine is running. This investigation illustrates the importance of surveillance in detecting and controlling injuries. Without such surveillance, the similarity among injuries reported on this paper would not have been recognized. Ongoing surveillance for injuries might identify other clusters of injuries.

ON DECEMBER 24, 1982, a record snowfall of 24 to 36 inches blanketed the Denver metropolitan area. Because increased deaths attributable to ischemic heart disease and hypothermia had been identified in previous investigations of the public health aspects of snow disasters (*1-3*), we attempted to evaluate the possible health effects of this Christmas Eve storm. We reviewed emergency room records of local hospitals for the week before and after the storm.

Our review identified a cluster of finger amputations and lacerations that occurred in the week following the storm. Further investigation revealed that snowblower use was associated with most of these serious finger injuries and that certain changes in the design of snowblowers might prevent these injuries.

Perhaps the most important finding from the study is that the cluster of injuries would not have been identified if this special surveillance activity